IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

JOSEPH C. COLACICCO, Individually and as Executor of the Estate of Lois Ann Colacicco, deceased,	)	
Plaintiff,	)	
v.	)	Civil Action No. 05-CV-05500-MMB
APOTEX, INC.; APOTEX CORP. as Subsidiary of Apotex, Inc.; and SMITHKLINE BEECHAM, doing business as GlaxoSmithKline,	)	
Defendants.	)	

BRIEF FOR *AMICUS CURIAE*
THE UNITED STATES OF AMERICA

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This brief is submitted pursuant to 28 U.S.C. § 517 and this Court's order of April 19, 2006.

The plaintiff in this litigation seeks to impose tort liability on drug manufacturers for failure to warn of an alleged danger, notwithstanding the Food and Drug Administration's (FDA's) repeated determination during the relevant period that there was not an adequate scientific basis for such a warning. The Court has requested FDA's views on preemption, including specifically the extent to which a court may consider agency views on preemption articulated in the course of a rulemaking that post-dates the conduct giving rise to this litigation. The Court has also inquired about the administrative law requirements, if any, applicable to agency views articulated in a preamble to a final rule.

Although FDA has the deepest sympathy for the plaintiff because of the loss of his wife, it is vital to ensure that state tort law does not undermine FDA's authority to protect the public health through enforcement of the prohibition against false or misleading labeling of drug products in the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 301 *et seq.* (FDCA). To base a tort judgment on drug manufacturers' failure to warn in October 2003 of an association between adult use of paroxetine hydrochloride and suicide or suicidality, despite FDA's judgment at that time that there was not reasonable evidence of such an association, would be to demand a warning statement that would have been false or misleading, and thus contrary to federal law. In such a case, federal law must prevail.

The preemption principles that require dismissal of the plaintiff's failure-to-warn claims are well-established, and have been recognized by FDA both in rulemaking and in other contexts, dating back long before the events giving rise to this litigation. As the Supreme Court has recognized, it is entirely appropriate for a court applying principles of federal preemption to

consider an agency's assessment of its regulatory interests and the extent to which state tort liability would conflict with those interests, even if — which is not the case here — the agency's views are set out after the operative events in question, mark a change in agency position, and are expressed in an amicus brief or other public statement that is not the product of notice-and-comment rulemaking. To the extent that the preamble to the final labeling rule promulgated in 2006 bears on this case, it is appropriately considered by the Court.

Nevertheless, in responding to this Court's inquiries regarding the operative effect of the preamble to the 2006 rule, FDA believes it important to emphasize that the basis for federal preemption in this litigation is not the preamble itself. The agency actions that are the basis for federal preemption in this litigation are FDA's repeated determinations between 1991 and 2003 that reasonable evidence did not support a warning on the label for paroxetine hydrochloride of an association between adult use of the drug and suicide or suicidality. As we next explain in greater detail, those labeling decisions should be given full force and effect under the Supremacy Clause.

STATUTORY AND REGULATORY BACKGROUND

A. FDA is the expert federal agency charged by Congress with regulating the manufacture, sale, and labeling of prescription drug products.[1] In particular, FDA has been charged by Congress with ensuring that drugs sold in the United States are safe and effective, 21

[1] FDA is a component of the United States Department of Health and Human Services (HHS). The Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 301 *et seq.* (FDCA), vests regulatory and enforcement authority in the Secretary of Health and Human Services. The Secretary has delegated this authority to the Commissioner of FDA. FDA Staff Manual Guides, Vol. II, § 1410.10 (available at http://www.fda.gov/smg/1410_10.html).

U.S.C. § 355(d) and § 393(b)(2)(B), and that they are not misbranded, 21 U.S.C. §§ 331(a), (b), and (k), 352, and 321(n).

In order to obtain FDA approval to market a new innovator drug, a manufacturer must submit a New Drug Application. *See* 21 U.S.C. § 355(b). The manufacturer must provide "full reports of investigations which have been made to show whether or not such drug is safe for use and * * * effective in use." *Id.* § 355(b)(1)(A). The manufacturer must also provide "specimens of the labeling proposed to be used for such drug." *Id.* § 355(b)(1)(A). The application will be denied if the manufacturer does not provide, *inter alia*, "adequate tests * * * to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof." *Id.* § 355(d)(1).

Once an innovator drug has been approved for sale, a drug manufacturer may seek approval under the FDCA to market a generic drug. The approval process for a generic drug is abbreviated, and does not require the manufacturer to show independent evidence of efficacy or safety. Instead, the manufacturer must show that the generic drug generally has the same active ingredients as an approved drug and is bioequivalent to that drug. *See* 21 U.S.C. § 355(j)(2)(A)(ii), (iv). The manufacturer must also show that the "labeling proposed for the [generic] drug is the same as the labeling approved for" the innovator drug. *Id.* § 355(j)(2)(A)(v). The only labeling changes permitted to be made are changes to reflect a different manufacturer or that the generic drug has "a different active ingredient" or a different "route of administration, dosage form, or strength" from the innovator drug. *See id.* § 355(j)(2)(A), (j)(2)(C).

Following FDA approval to market a drug, drug manufacturers are subject to continuing obligations under the FDCA. *See* 21 U.S.C. § 355(k); 21 C.F.R. § 314.80, 314.98. A manufacturer must keep a record of any "adverse event associated with the use of a drug in humans, whether or not considered drug related," and must periodically report these adverse events to FDA. *See* 21 C.F.R. §§ 314.80(a), (c), 314.98(a). For adverse events that are "serious and unexpected," the manufacturer is required to report the event to FDA within 15 days after learning about the event, and is also required to conduct an investigation of each event and to provide follow-up information to FDA. *See* 21 C.F.R. § 314.80(c)(1).

B. The preemption issue raised by the Court's letter implicates the labeling provisions of the FDCA, as implemented by FDA. Under the FDCA, a drug is unlawfully misbranded when its labeling is false or misleading in any particular, or does not provide adequate directions for use or adequate warnings against any use dangerous to health. *See* 21 U.S.C. § 331(a), (b), and (k); *id.* § 352(a), (f), (j); *id.* § 321(n). A prescription drug satisfies FDA labeling requirements if the drug manufacturer gives physicians and pharmacists sufficient information, including indications for use and "any relevant hazards, contraindications, side-effects, and precautions," to allow those medical professionals to "use the drug safely and for the purposes for which it is intended * * *." 21 C.F.R. § 201.100(c)(1). Under federal law, therefore, the evaluation of a drug's safety and effectiveness is inextricably linked with the drug labeling. *See also* 50 Fed. Reg. 7452, 7470 (1985) ("Drug labeling serves as the standard under which FDA determines whether a product is safe and effective.").

FDA regulations set forth specific requirements for prescription drug labeling. *See* 21 C.F.R. Part 201, Subparts A, B, and G. Prescription drug labels must contain "a summary of the

essential scientific information needed for the safe and effective use of the drug," which includes indications for use as well as a description of "serious adverse reactions and potential safety hazards" associated with use of the drug. 21 C.F.R. §§ 201.56(a), 201.57(c), (e). The labeling regulations are designed to require warnings of all known risks based on reliable scientific evidence. *See* 21 C.F.R. § 201.56(c), 201.57(c), (e) (requiring as a condition of a warning that there be "reasonable evidence of an association of a serious hazard with a drug").

As noted above, applications for both innovator drugs and generic drugs must include copies of the proposed labeling. For innovator drugs, FDA considers evidence submitted by the applicant, as well as other relevant scientific information known to the agency, to determine whether the label is accurate, truthful, and adequate. FDA and drug manufacturers discuss in detail the proposed drug labeling, including the various warnings to be placed on the product. Based on the known scientific evidence, appropriate warnings are drafted that identify established risks while avoiding inadequately substantiated risks, mention of which could improperly deter use of the drug to the detriment of the very patients it is designed to benefit. When FDA approves a new drug application for an innovator drug, it also approves the precise final version of the drug labeling, including even the type size and font to be used by the manufacturer in that labeling.

For generic drugs, FDA confirms as a condition of approval that, with exceptions not applicable here, the labeling is the same as the labeling approved for the innovator drug for which the drug is a generic form. 21 U.S.C. § 355(j)(4)(G). As noted above, generic drug manufacturers are required to use labeling that is, for all relevant purposes here, identical to the approved labeling for the innovator drug.

After a drug has been approved, a manufacturer may not deviate from FDA-approved product labeling, except in limited circumstances set forth in FDA regulations. For the manufacturer of an innovator drug who wishes to add or strengthen a warning statement on the approved labeling, the manufacturer may provide FDA with a supplemental submission regarding the proposed labeling change, providing a full explanation of the basis for the proposed change. *See* 21 C.F.R. § 314.70(c)(1), (3), (6)(iii)(A).[2] If the FDA has not rejected the supplement within 30 days after its submission, the manufacturer may distribute the drug with the new proposed labeling — although FDA may choose to reject the proposed labeling change even after this date, and may also order the drug manufacturer to cease distributing the drug with the new labeling. *See* 21 C.F.R. § 314.70(c)(7).

For a generic drug manufacturer, there is no statutory or regulatory provision permitting the manufacturer to make a labeling change to its generic drug without prior FDA approval. To the contrary, a generic drug manufacturer is required to conform to the approved labeling for the listed drug. *See* 21 C.F.R. § 314.150(b)(10); *see also* 57 Fed. Reg. 17,950, 17,961 (1992). If a generic drug manufacturer believes that new safety information should be added to the label for the drug, the manufacturer must contact FDA with "adequate supporting information." 57 Fed. Reg. at 17,961. The FDA will consider this information and will make a determination whether the labeling for both the generic drug *and* the innovator drug should be revised. *Id.*

C. This litigation involves the drug paroxetine hydrochloride, which is the active ingredient of the brand-name drug Paxil. FDA approved GlaxoSmithKline's new drug

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[2] Indeed, if the drug manufacturer has "reasonable evidence of an association of a serious hazard with a drug," the manufacturer has an obligation to seek FDA approval for a labeling change, in order to add a warning of the new potential hazard. *See* 21 C.F.R. § 201.57(e).

application for Paxil in 1992, and the drug is currently approved to be marketed for use in treating major depressive disorder, obsessive compulsive disorder, panic disorder, social anxiety disorder, generalized anxiety disorder, and posttraumatic stress disorder. Apotex Corp. received approval in 2003 to market its generic form of paroxetine hydrochloride. Paroxetine hydrochloride is in the class of drugs known as "selective serotonin reuptake inhibitors" (SSRIs), which are used to treat depression and other psychological disorders.

In order to evaluate the safety and efficacy of paroxetine hydrochloride and other SSRIs in treating depression, and to ensure that warning statements in the labeling are accurate and not misleading, FDA must distinguish between events that result from use of the drug and those resulting from the underlying disease. Drawing that distinction is most difficult where, as in the case of depression treated with an SSRI, the adverse events in question — suicide and suicidality — are also a known consequence of the treated disease.

Since 1992, the FDA-approved label for Paxil (and, subsequently, generic forms of paroxetine hydrochloride approved for marketing) has reflected the risk of suicide in patients using the drug. The original approved label warned that "[t]he possibility of a suicide attempt is inherent in major depressive disorder and may persist until significant remission occurs." The label recommended "[c]lose supervision of high-risk patients" in addition to drug therapy, and also indicated that prescriptions for Paxil "should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose." Attachment to FDA Approval Letter, NDA 20-031/S029, at 12.

Prior to October 2003, however, FDA had repeatedly determined, based on its scientific analysis of available information, that there was inadequate evidence of an association between

use of Paxil or other SSRIs by adult patients and a risk of suicide or suicidality to support a specific warning in the "Precautions" section of the drug's labeling.

In July 1991, the FDA denied a citizen petition seeking FDA withdrawal of approval for Prozac, based on FDA's conclusion that "[t]he data and information available at this time do not indicate that Prozac causes suicidality or violent behavior." July 26, 1991, letter from FDA to S. Block, at 1 (copy attached at Exhibit A).

In September 1991, FDA's Psychopharmacological Drugs Advisory Committee met and, after hearing more than four hours of testimony and reviewing and discussing relevant scientific studies, voted unanimously that there was no "credible evidence to support a conclusion the antidepressant drugs cause the emergence and/or intensification of suicidality and/or other violent behaviors," and no evidence "to indicate that a particular drug or drug class poses a greater risk [than other anti-depressant drugs] for the emergence and/or intensification of suicidal thoughts and acts and/or violent behaviors." Dep't of Health and Human Servs., Public Health Service, Food and Drug Administration, Psychopharmacological Drugs Advisory Committee, Sept. 20, 1991, Transcript at 302 (copy attached as Exhibit B). The Committee voted against any labeling change to warn against the risk of suicide or suicidality as a result of Prozac use. *See id.* at 331-332.[3]

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[3] The head of FDA's Psychopharmacology Unit explained to the Advisory Committee at the 1991 meeting that FDA had received reports of adverse events regarding users of Prozac, and had determined that the terms "suicidal ideation" and "violent behaviors" should be added to the subsection of adverse reactions entitled "Post-Introduction Reports." FDA had explicitly decided at that time that the terms should not be listed in the "Precautions" section of the labeling, however, because of the agency's "lack of confidence in a causal link between the taking of the drug and those behaviors." Exh. B., at 136-137.

In 1992 and 1997, FDA denied citizen petitions requesting that FDA revise the approved labeling for Prozac to include a warning of suicide or suicidal thought. *See* June 3, 1992, letter from FDA to I. Hellander (copy attached as Exhibit C); June 25, 2997, letter from FDA to R. Meysenburg (copy attached as Exhibit D). In its 1992 response, FDA explained that the "currently available, relevant evidence" was "not sufficient to reasonably conclude that the use of Prozac is possibly associated with suicidal ideation and behavior." Exh. C, at 1. FDA detailed the available scientific studies and case reports, and concluded that they did "not permit a conclusion that Prozac, as opposed to the conditions for which Prozac was administered," was responsible for suicidal thought. Exh. C, at 3. As FDA noted, its own advisory committee had recently concluded "that the evidence was not strong enough to justify the suggestion of even the possibility of a causal linkage in the labeling." Exh. C, at 15. FDA reached the same conclusion in 1997, noting that, although the agency had received numerous drug experience reports concerning Prozac and suicidal ideation and suicidality, the agency had determined after careful consideration "that no labeling revisions were warranted" as of that date, and that then-current labeling for Prozac "appropriately reflect[ed] the level of concern about Prozac and suicidality." Exh. D, at 2.

In 2002, FDA conducted a review of SSRIs, in order to evaluate the current state of scientific knowledge regarding a connection between the use of SSRIs and suicide. *See* Andrew D. Mosholder, Medical Officer, FDA Division of Neuropharmacological Drug Products, *Mortality and Suicide Rates in Randomized Controlled Trials of Psychiatric Drugs: Update 2002*, 42nd Annual National Institute of Mental Health's New Clinical Drug Evaluation Unit Meeting (June 10-13, 2002) (copy of slide presentation attached as Exhibit E). After reviewing

studies involving randomized controlled trials of psychiatric drugs, the agency concluded that the scientific evidence did not show an association between the use of anti-depressants, including SSRIs, and suicide. *See* Exh. E, at 35 (summarizing agency's finding that "[t]here were no significant differences in suicide rates between active treatments and placebo" for patients with major depressive disorder, schizophrenia, or dementia).

In May 2003, FDA received a report from GlaxoSmithKline suggesting that *pediatric* patients who used Paxil were at an increased risk for suicide and suicidality. Based on this report and FDA's subsequent internal analysis, FDA issued a public health advisory in October 2003 for *pediatric* users of Paxil, explaining that preliminary data suggested an excess of reports for suicidality in pediatric patients with major depressive disorder. *See* www.fda.gov/cder/drug/ advisory/mdd.htm. However, FDA declined to warn of any similar risk for *adult* patients at that time, merely emphasizing that — as already indicated by the labeling for Paxil and Apotex's generic form of paroxetine hydrochloride — all patients treated with antidepressant drugs for major depressive disorder face a risk of suicide and should be closely supervised. *See id.*; FDA Talk Paper, T03-70, Oct. 27, 2003, www.fda.gov/bbs/ topics/ANSWERS/2003/ans01256.html.

In March 2004, for the first time, FDA issued a public health advisory directing manufacturers of ten SSRIs, including Paxil, to include stronger cautions and warnings on drug labels about the need to monitor adult patients for signs of worsening depression or suicidality. *See* FDA Talk Paper, www.fda.gov/bbs/topics/ANSWERS/2004/ANS01283.html; FDA Public Health Advisory, www.fda.gov/cder/drug/AntidepressanstPHA.htm. Even as of that date, FDA emphasized that it had "not concluded that these drugs cause worsening depression or suicidality" in adult patients, or that certain symptoms associated with antidepressant use in

some adult patients — including agitation and akathisia (severe restlessness) — were a precursor to worsening depression or suicidality. FDA Public Health Advisory; *see also* FDA, Questions and Answers on Antidepressant Use in Children, Adolescents, and Adults, www.fda.gov/cder/drug/antidepressants/Q&A_antidepressants.htm. Currently, FDA is engaged in a comprehensive scientific review of existing studies, involving hundreds of clinical trials and thousands of adult patients, to determine whether there is an increased risk of suicide or suicidal behavior in adults treated with antidepressant drugs. *See* FDA Public Health Advisory, www.fda.gov/cder/drug/advisory/WWRI200507.htm; *see also* FDA Talk Paper, July 1, 2005, www.fda.gov/bbs/topics/ANSWERS/2005/ANS01362.html.[4]

D. Between October 6 and October 18, 2003, Lois Ann Colacicco was treated with paroxetine hydrochloride manufactured by Apotex. On October 28, 2003, at the age of 55, she committed suicide.

Ms. Colacicco's husband brought this lawsuit in federal court under state law against Apotex, the manufacturer of the paroxetine hydrochloride taken by Ms. Colacicco, and GlaxoSmithKline, the manufacturer of the brand-name drug. Mr. Colacicco alleges that his wife was inadequately informed of the adverse effects of the drug, and specifically that Apotex and/or GlaxoSmithKline failed to provide adequate warnings to potential users that the drug could

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[4] On May 8, 2006, GlaxoSmithKline announced that, based on a meta-analysis of studies of Paxil that the company completed in 2006, GlaxoSmithKline had discovered a higher incidence of suicidal behavior in adult patients with major depressive disorder treated with paroxetine compared with placebo, as well as a higher incidence of suicidal behavior in young adults treated with paroxetine compared with placebo. *See* http://www.gsk.com/media/paroxetine_adult.htm. GlaxoSmithKline has filed a supplemental submission with FDA seeking approval for a new warning on the label for Paxil that "young adults, particularly those with depression, may be at an increased risk of suicidal behavior (including suicide attempts) when treated with PAXIL."

cause suicidality, violence, and aggression. Mr. Colacicco also alleges that Apotex and/or GlaxoSmithKline failed to adequately inform FDA, physicians, and potential users that Paxil is not effective to treat depression in some adult users, and causes an increased risk of suicide and suicidality in some adults. In addition to alleging that the defendants are liable for failure to provide adequate warnings, Mr. Colacicco seeks to impose liability for breach of warranty, fraud, negligent misrepresentation, intentional and negligent infliction of emotional distress, negligence, negligence *per se*, strict product liability, wrongful death, and violation of state consumer protection laws.[5]

The defendants sought dismissal on numerous grounds, including federal preemption. Following briefing by the parties on the defendants' motions to dismiss, the district court directed the parties and, subsequently, FDA, to provide views regarding the applicability in this litigation of the preamble to FDA's recent rule on drug labeling, 71 Fed. Reg. 3922 (2006), the validity of the preamble as a rule of decision, and whether it would be impermissibly retroactive to apply the policy set out in the preamble to claims arising out of conduct that predated the preamble's issuance. On May 4, 2006, the Court sent FDA an additional letter, asking for details regarding any potential change in agency position regarding preemption, as well as opportunities for public comment on the agency's position.

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[5] At this early stage of the proceedings, and in light of the plaintiff's primary reliance on the theory that defendants are liable for failure to include a warning on their drug labeling in October 2003 of an asserted association between paroxetine hydrochloride and adult suicide or suicidality, FDA has focused on that failure-to-warn theory in its discussion of federal preemption. The agency takes no position on the viability of the plaintiff's other claims, or the potential applicability of federal preemption to those claims.

ARGUMENT

I. FEDERAL LAW PREEMPTS A STATE TORT CLAIM ARISING OUT OF DRUG MANUFACTURERS' ALLEGED FAILURE TO PROVIDE A WARNING THAT FDA HAD DETERMINED WAS NOT SCIENTIFICALLY SUPPORTED.

A. FDA's scientific judgment in October 2003, when paroxetine hydrochloride was prescribed to, and taken by, Ms. Colacicco, was that there was no reasonable evidence available at that time of an association between adult use of the drug and suicide or suicidality. To include on a drug's label a warning about a drug's effects, when FDA has determined that such a warning is not based on reliable scientific evidence, would be "false or misleading," 21 U.S.C. §§ 352(a), (f), and would constitute unlawful misbranding. 21 U.S.C. § 331(a), (b), and (k). Under the Supremacy Clause (U.S. Const. art. VI, cl. 2), a state may not cause a drug manufacturer to choose between compliance with federal law and state tort liability. *See Geier v. American Honda Motor Co.*, 529 U.S. 861, 873 (2000) (Supremacy Clause forbids "'conflicts' that make it 'impossible' for private parties to comply with both state and federal law"). Necessarily, therefore, federal conflict preemption bars Mr. Colacicco's attempt to impose liability under state tort law for defendants' alleged failure to provide a warning for Paxil or its generic equivalent that would have violated federal drug labeling provisions.

In considering the agency's views on drug labeling, it is critical to understand that, where warnings are concerned, more is not always better. FDA's requirement that a warning must be scientifically substantiated is designed to ensure each drug's optimal use. Under-use of a drug based on dissemination of unsubstantiated warnings would deprive patients of efficacious, possibly lifesaving treatment, thereby undermining the benefits of federal regulation. Further, allowing unsubstantiated warnings would likely diminish the impact of valid warnings by

creating an unnecessary distraction and making even valid warnings less credible. In this respect, the plaintiff's assertion that "[f]ederal prescription drug labeling regulations are merely 'minimum standards,'" Docket No. 17-3, is erroneous.

Rather than set minimum standards for warnings in drug labeling, FDA seeks to encourage the optimal level of use in light of reasonable safety concerns, by requiring scientific evidence of an association between a drug and a particular hazard before warning of that association on a drug's labeling. *See* 21 C.F.R. § 201.57(e). Notably, the plaintiff does not argue that the label for paroxetine hydrochloride failed to make physicians aware of the possible risk of suicide or suicidality in patients treated with the drug. From 1992 onward, the label explicitly warned about the "possibility of a suicide attempt," and cautioned treating physicians to undertake "[c]lose supervision of high-risk patients."

The plaintiff nonetheless asserts that manufacturers of Paxil or its generic equivalent should have warned of an "increased risk" of suicide or suicidality in adults taking Paxil and other SSRIs. *See, e.g.,* Complaint ¶¶ 28-29, 34, 50, 68. During the relevant period for purposes of this litigation, however, FDA had specifically and repeatedly rejected claims that adult use of SSRIs was associated with an increased risk of suicide or suicidality. *See* pp. 7-10, *supra.* In responses to citizen petitions, in its internal review of scientific studies, and in its advisory committee meetings, FDA repeatedly concluded that the available scientific evidence did not support an association between adult SSRI use and suicide. FDA specifically rejected, during this time period, proposed warnings of such an association.

Under these circumstances, and in light of the agency's judgment as of October 2003 that there was not reasonable evidence of an association between adult use of paroxetine chloride and

suicide or suicidality, any warning of such an association would have been barred as a matter of federal law. Although FDA regulations permit a "pioneer" new drug manufacturer to submit a supplement to add or strengthen a warning on a label, and to carry out that change without waiting for prior FDA approval, the regulations also require the innovator manufacturer to provide "a full explanation of the [scientific] basis for the change," and do not alter the statutory requirement that a manufacturer may not misbrand a drug. *See* 21 C.F.R. § 314.70(c)(3), (6)(iii); 21 U.S.C. § 331(a), (b), and (k). As of October 2003, any warning of an association between adult use of paroxetine hydrochloride and suicide or suicidality would have been deemed "misleading" and, thus, a violation of federal law. *See* 21 U.S.C. § 352(a), (f). Accordingly, the Supremacy Clause precludes the imposition of liability under state law for the failure to provide such warning. *See, e.g., Hurley v. Lederle Labs.*, 863 F.2d 1173, 1179 (5th Cir. 1988); *see also Geier*, 529 U.S. at 881-882.[6]

B. The plaintiff suggests that state tort liability for failure to warn is permissible unless FDA has explicitly prohibited a manufacturer from warning about suicidality or aggression on the label for paroxetine hydrochloride. As the Supreme Court held in *Geier*, however, there is no requirement of "a specific, formal agency statement identifying conflict" for preemption to apply. 529 U.S. at 884. Rather, the operative question is whether a tort suit would "stand[] as an obstacle to the accomplishment and execution" of the objectives of federal law. *Hines v. Davidowitz*, 312 U.S. 52, 67 (1941).

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[6] As explained in further detail below, furthermore, submitting a supplement application and changing the drug labeling prior to FDA approval was not an available option to a generic drug manufacturer such as Apotex. *See* pages 16-17, *infra*.

In the context of drug labeling, Congress has authorized FDA to apply its scientific expertise to determine, in the first instance, what warnings are appropriate and necessary for a particular drug. *See Henley v. FDA*, 77 F.3d 616, 621 (2d Cir. 1996); *Public Citizen Health Research Group v. Commissioner*, 740 F.2d 21, 28 (D.C. Cir. 1984). Given FDA's repeated determinations during the relevant time that it would be inappropriate to warn of an association between adult use of paroxetine hydrochloride and suicide or suicidality, it would stymie the regulatory scheme established by Congress to hold as a matter of state law that the defendants are liable for failing to provide such an inappropriate warning.[7] Judicial imposition of liability for failure to warn would interfere with FDA's ability to protect the public from unsubstantiated warnings that would deter appropriate uses of a drug and diminish the impact of valid warnings. Even if compliance with both state and federal law in such an instance would not be impossible, state tort liability would pose a sufficient threat to federal regulatory objectives to support preemption under the Supremacy Clause. *See, e.g., Geier*, 529 U.S. at 884-885; *Jones v. Rath Packing Co.*, 430 U.S. 519, 543 (1977).

C. The plaintiff's failure-to-warn claims against Apotex Corporation and its parent company, Apotex, Inc. (collectively, Apotex), are preempted for the additional reason that the claims seek to impose liability on Apotex for its alleged failure to provide a warning that, as a generic drug manufacturer, Apotex was barred from giving without prior FDA approval.

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[7] In determining the proper role for state law in this context, furthermore, it is significant that the federal government has been regulating the manufacture and sale of drugs since 1906. As the Supreme Court recognized in *United States v. Locke*, 529 U.S. 89 (2000), any presumption against federal preemption "is not triggered when the State regulates in an area where there has been a history of significant federal presence." *Id.* at 108.

The plaintiff claims that Apotex had a duty to modify the label for paroxetine hydrochloride to add a warning regarding a risk of suicide. *See, e.g.,* Complaint ¶¶ 50, 86, 102(c). Elaborating on this legal theory in his response to Apotex's motion to dismiss, the plaintiff argues that Apotex should have filed a supplement to its application under 21 C.F.R. § 314.70(c), which allegedly would have permitted Apotex to provide the warning that the plaintiff claims should have been given.

Under federal law, however, generic drug labels are required to replicate the warnings contained in the approved labeling for the innovator, or name-brand, drug. *See* 21 U.S.C. §§ 355(j)(2)(A)(v), (j)(2)(C); 21 C.F.R. § 314.150(b)(10). Accordingly, a generic drug manufacturer is not permitted to add a warning or caution to the label without prior approval from FDA. If a generic drug manufacturer "believes that new safety information should be added" to the product's labeling, the manufacturer must "provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and [innovator] drugs should be revised." 57 Fed. Reg. at 17,961. Only if the FDA directs that the labels for *both* the generic and the innovator drugs should be changed, can the generic drug manufacturer add a new warning or caution to the labeling for its drug.

For the reasons we have already explained, if Apotex had approached FDA in or prior to October 2003 to seek approval for a warning regarding suicide or suicidality on the label for paroxetine hydrochloride, FDA would have rejected the warning as scientifically unsupported. For this reason, as well, the failure-to-warn claims against Apotex are preempted by federal law.

II. FDA'S VIEWS ON PREEMPTION ARE PROPERLY CONSIDERED BY THIS COURT.

A. As we have explained, principles of conflict preemption bar the plaintiff's attempt to impose state tort liability on defendants for the asserted failure to provide a drug label warning in October 2003 that had been rejected as unsupported by FDA during the period in question. The same preemption principles are recognized in the preamble to the final rule adopted by FDA in January 2006. *See* 71 Fed. Reg. 3922, 3934 (noting that federal law preempts state-law labeling requirement that conflicts with or is contrary to FDA-approved labeling, and criticizing litigant's claim that a drug manufacturer has a state-law duty to label products "with specific warnings that FDA had specifically considered and rejected as scientifically unsubstantiated").

As we have explained, the 2006 preamble is not itself the basis for federal preemption, which is triggered by FDA's repeated determinations prior to October 2003 that there was insufficient scientific evidence of an association between adult use of SSRI and suicide or suicidality to permit a warning on the labeling for those drugs. The plaintiff has not argued that FDA's labeling decisions were outside the scope of its statutory authority. Under these circumstances, implied conflict preemption bars state tort liability for failure to provide a warning as of October 2003 that had been rejected by FDA, regardless whether FDA explicitly claimed that its labeling decisions would have preemptive effect.

Nevertheless, the 2006 preamble sets out FDA's current understanding of the way in which a state tort judgment can interfere with FDA's implementation of federal law, and thus is properly considered by this Court. In proposing a new rule governing the format and content of drug labeling — a rule that did not itself explicitly preempt state law — FDA received comments about the product liability implications of the proposed rule. The Administrative Procedure Act

requires FDA to address the comments it receives, and FDA did so by explaining its view of the law of implied conflict preemption.[8]

Although the plaintiff has suggested that any argument for federal preemption of his failure-to-warn claims would constitute a wholesale change in agency position, in fact FDA has filed briefs dating back to at least 2000 taking the position that the Supremacy Clause bars state tort liability for failure to include a warning on a drug label that is in conflict with or contrary to the warnings approved by FDA. *See, e.g., Kallas v. Pfizer, Inc.*, No. 2:04cv0998 (D. Utah. filed Sept. 15, 2005) (explaining that drug manufacturer may not be held liable for failure to warn of association between pediatric use of Zoloft or other SSRIs and suicide, where FDA had determined at relevant time that there was not reasonable evidence of such an association); *Motus v. Pfizer, Inc.*, No. 02-55498, Amicus Brief for United States (9th Cir. filed Sept. 3, 2002) (explaining that drug manufacturer may not be held liable for failure to warn of alleged danger where FDA had made contemporaneous determination that there is no scientific basis for such warning); *Bernhardt v. Pfizer, Inc.*, No. 00 Civ. 4042 (LMM), Statement of Interest of United States (S.D.N.Y. filed Nov. 13, 2000) (explaining that federal law preempts state claims seeking to require additional warnings on drug labels, and emphasizing that approval of drug labels is within primary jurisdiction of FDA).

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[8] Neither the Administrative Procedure Act nor Executive Order 13,132 requires FDA to provide notice of and an opportunity to comment on responses to public comments about a proposed rule, setting forth the agency's view of principles of implied conflict preemption in a preamble that is not part of the codified final rule. Nevertheless, in adopting the final rule in 2006, FDA did consult with a number of organizations representing the interests of state and local governments about the potential interaction between FDA drug labeling requirements and state law. *See* 71 Fed. Reg. 3922, 3969 (2006).

Furthermore, FDA rules dating back to at least 1979 reflect the agency's views that the ultimate decision whether to require a warning on a drug label rests with FDA, and that federal law prohibits inclusion of statements on a label that FDA has determined not to be supported by substantial evidence. *See, e.g.,* 44 Fed. Reg. 37,434, 37,435, 37,441, 37,447 (1979). A fortiori, where state law seeks to impose a conflicting or contrary requirement, it must be preempted.

The Court inquired about the significance of a 1998 preamble to a final rule, in which FDA explained that a regulation providing for FDA approval of patient labeling for a limited number of products was "not intended to preclude the states from imposing additional labeling requirements." 63 Fed. Reg. 66,378, 66,384 (1998). However, nothing in that preamble suggests that where, as here, FDA has rejected a warning proposed for a drug's labeling as lacking an adequate scientific basis, that warning may nonetheless be required by operation of state law. To the contrary, the 1998 preamble explicitly recognized that state law cannot "alter" FDA-required labeling. *Id.* To the limited extent that the 1998 preamble might be relevant to this litigation, therefore, it supports application of federal preemption to the plaintiff's failure-to-warn claims in this litigation.[9]

B. The Supreme Court has repeatedly recognized that, in determining whether federal preemption bars a state-law claim, it is appropriate to consider a federal agency's views regarding conflict — even if those views are expressed for the first time in the course of litigation or otherwise post-date the events giving rise to the claim. The Supreme Court has also

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[9] Similarly, although the 2006 letter from three individual Members of Congress to FDA, appended to the plaintiff's March 27, 2006, letter to the Court, asserts that FDA has recently changed its position on preemption, that letter explicitly acknowledges that, under FDA's pre-2006 approach, federal law was considered to preempt conflicting state-law requirements. *See* Doc. 38, Exh. A-3.

held that the agency is not required to set out its views in a rule adopted after notice-and-comment rulemaking in order for those views to be given weight in the preemption analysis.

In *Geier*, for example, the Court explicitly relied on the Department of Transportation's explanation in an amicus brief regarding the agency's regulatory objectives, and the agency's conclusion that state tort liability would interfere with the accomplishment of those objectives, in holding that state-law claims were barred by federal preemption. 529 U.S. at 883. As the Supreme Court emphasized, Congress had delegated to the agency the authority to implement the statutory scheme in a complex and technical area, and the agency was "likely to have a thorough understanding of its own regulation and its objections and [to be] 'uniquely qualified' to comprehend the likely impact of state requirements." *Id.* at 883 (quoting *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 496 (1996)).[10] Obviously, the amicus brief filed by the Department of Transportation in *Geier* post-dated the events claimed to give rise to liability. *See also Horn v. Thoratec Corp.*, 376 F.3d 163, 171, 176-177 & n.22 (3d Cir. 2004) (relying on views set out in FDA's amicus brief to hold that failure-to-warn claims regarding medical device are preempted).

Similarly, in *Fidelity Federal Savings & Loan Ass'n v. de la Cuesta*, 458 U.S. 141 (1982), the Court relied in part on an agency rule post-dating the events in question to conclude

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[10] The *Geier* Court noted that the agency's description of its regulatory objectives and the potential interference with those objectives posed by application of state law had been consistent over time. 529 U.S. at 883. The same is true, as we have explained, of FDA's view regarding federal preemption of state tort claims seeking to impose liability for failure to give a warning specifically considered and rejected by the agency. In any event, the fact that an agency's view on conflict preemption marks a change from an earlier position does not preclude a court's consideration of, and deference to, the agency's assertion that state-law liability would interfere with the accomplishment of federal regulatory objectives. *See Buckman v. Plaintiffs' Legal Committee*, 531 U.S. 341, 347-349, 354 n.2 (2001); *Hillsborough County v. Automated Med. Labs., Inc.*, 471 U.S. 707, 714-715 (1985); *Horn v. Thoratec Corp.*, 376 F.3d 163, 171 (3d Cir. 2004).

that state-law liability would interfere with the objectives of the federal regulatory scheme. *Id.* at 155-156. Indeed, in *Hillsborough County v. Automated Medical Laboratories, Inc.*, 471 U.S. 707 (1985), the Supreme Court suggested that federal preemption would apply despite an agency's explicit statement at the time it promulgated regulations that the regulations were not intended to have preemptive effect, if the agency subsequently changed its view on the strength of its interests in preemption or the effect of the regulations in question. *Id.* at 715, 721-722 & n.5.

The Supreme Court has also made clear that, in discussing the extent to which state law will interfere with federal regulatory objectives, an agency is not required to undertake notice-and-comment rulemaking for its views to be given weight by the Court. In *Geier*, the Court explicitly rejected such an argument, pointing out that requiring an agency to set out an explicit finding of conflict through formal rulemaking would permit "conflicts that an agency, and therefore Congress, is most unlikely to have intended." *Geier*, 529 U.S. at 885. In *Hillsborough County*, the Court recognized that an agency could express its views on preemption through a variety of sources, including "preambles" and "responses to comments." 471 U.S. at 718. Accordingly, to the extent that the 2006 preamble sheds additional light on FDA's view of the interference with the accomplishment of federal regulatory objectives that would result from state liability for failure to provide a warning rejected by the agency, the preamble is appropriately considered by this Court.

CONCLUSION

For the foregoing reasons, the Court should hold that the Supremacy Clause bars a state tort claim premised on defendants' failure to provide a warning in October 2003 of an association between adult use of paroxetine hydrochloride and suicide or suicidality.

Respectfully submitted,

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I hereby certify that on May 10, 2006, I caused two copies of the foregoing Brief for Amicus Curiae the United States of America and the accompanying Addendum to be served on the following counsel by overnight delivery, postage prepaid:

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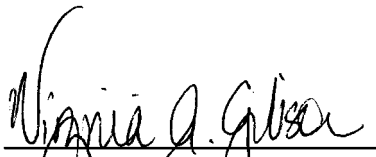

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